probable cause(s) of contamination. A corrective action plan is devised and implemented to eliminate the problem(s).

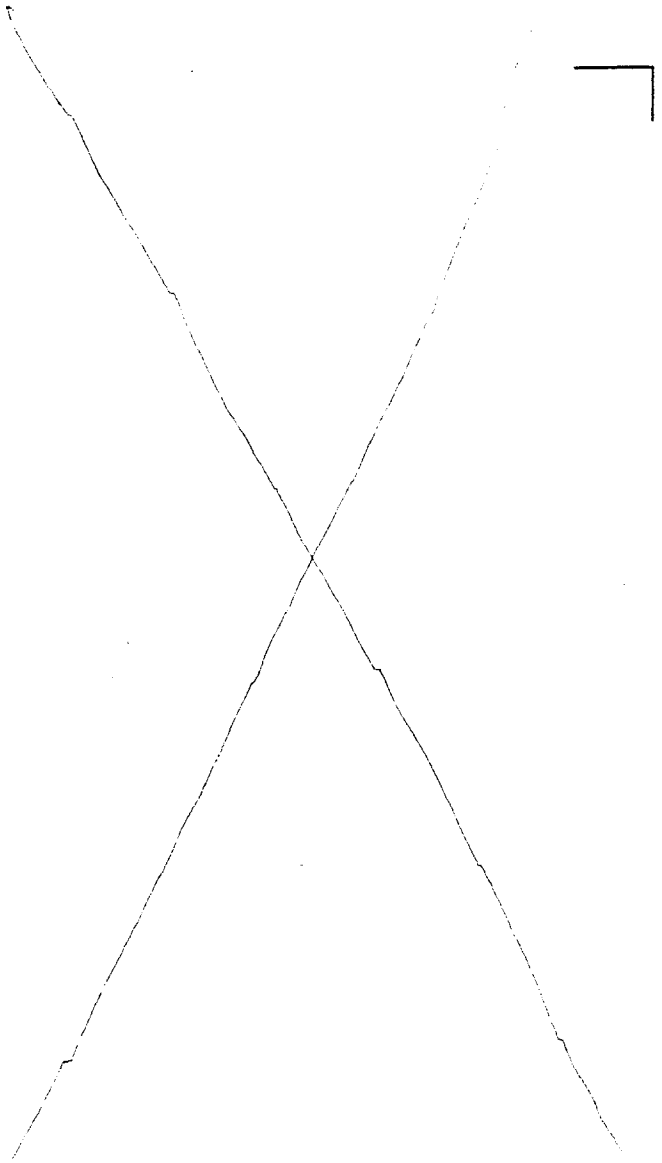
Drug Substance Purification

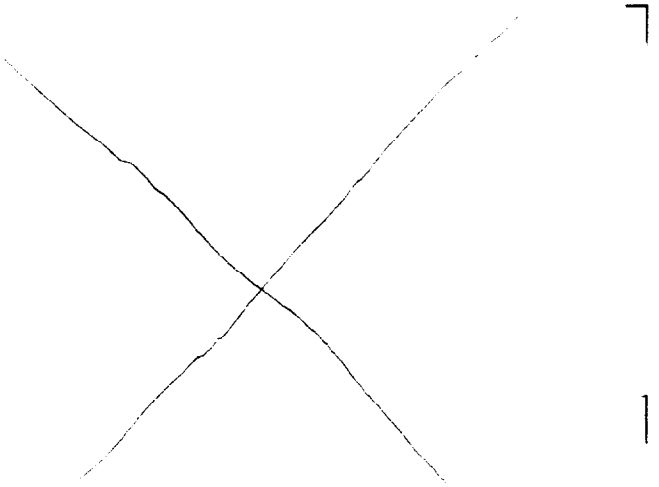
Taken from BLA Process Overview section 3.4.2 vol 1 and section 4.2.3.6 Description of the Purification and Formulation Process:

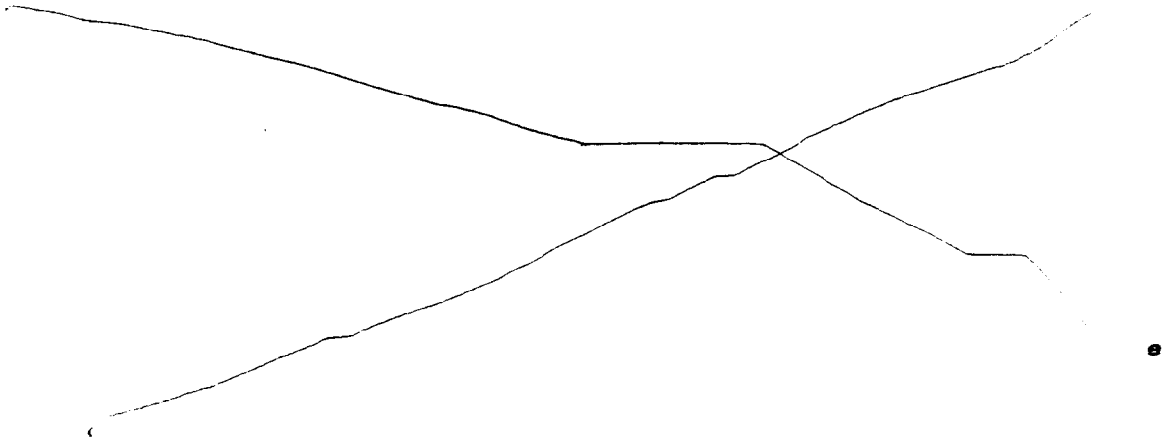
MEDI-493 is subsequently purified from the medium using a series of chromatography and filtration steps

The —— cation exchange step is a product capture step optimized for volume, and bovine serum albumin (BSA) and DNA reduction. BSA is the major protein component of the cell culture medium used at a level of —— Because of the high isoelectric point —— of MEDI-493 nucleic acids tend to co-purify such that chromatographic separations alone have not effectively reduced the DNA level to the pg/mg MEDI-493 range. For this reason,

process. Enzymatic treatment in combination with the downstream chromatography steps reduces the DNA content to < 1 pg/mg MEDI-493. Subsequent —— affinity chromatography removes the Benzonase in addition to other process and cell-derived contaminants. The nanofiltration step was shown by viral clearance studies to effectively remove a variety of viruses (Xenotropic Retrovirus, Pseudorabies Virus, Simian Virus 40, and Poliovirus) most notably small, chemically resistant, non-enveloped viruses such as Poliovirus. The —— treatment serves as a viral inactivation step. —— anion exchange chromatography further reduces process contaminants such as BSA. transferrin, and endotoxin, and the ——————————. Following Phenyl chromatography the product is formulated in 25 mM histidine, 1.2 mM glycine, 3% mannitol, pH 6.0 buffer. The resulting formulated bulk MEDI-493 is 0.2 micron filtered into







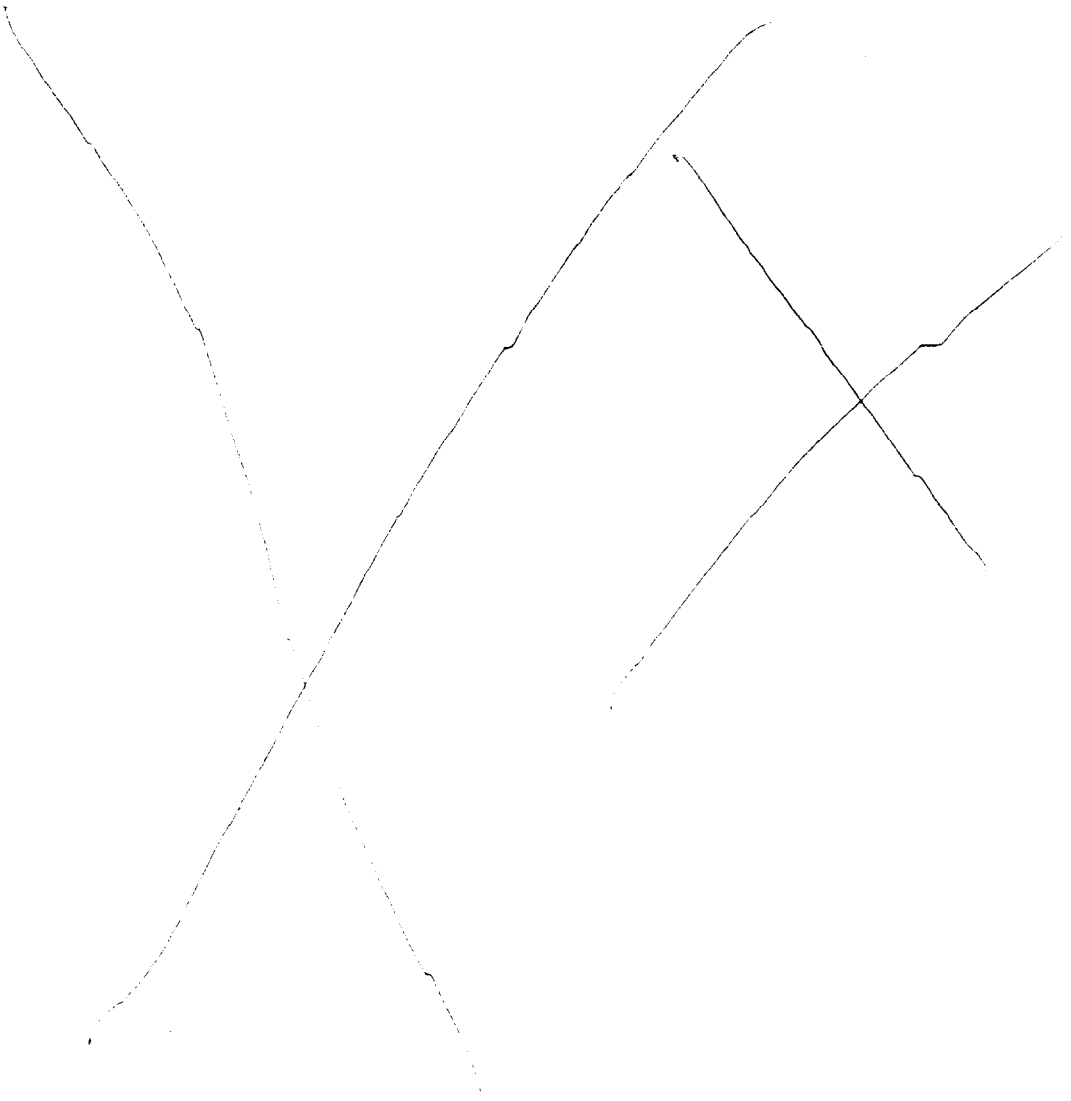
Purification Equipment

- The equipment used in the process are:
- Class Six Braided Silicone Tubing
- Filters
- 10, 20 and 30-inch
- : 30 and 40 Filters
- ter
- Conductivity Meters
- pH Meters
- Spectrophotometer
- Floor Scales
- Peristaltic Pumps
- Buffer Preparation Tanks, 200 L and 500 L
- Pellicon Ultrafiltration System
- Stainless Steel Pressure Cans
- Stainless Steel Tanks
- ller
- Sterile Filter(s)
- Ultrafiltration System

- Horizontal Laminar Flow Hood

Materials

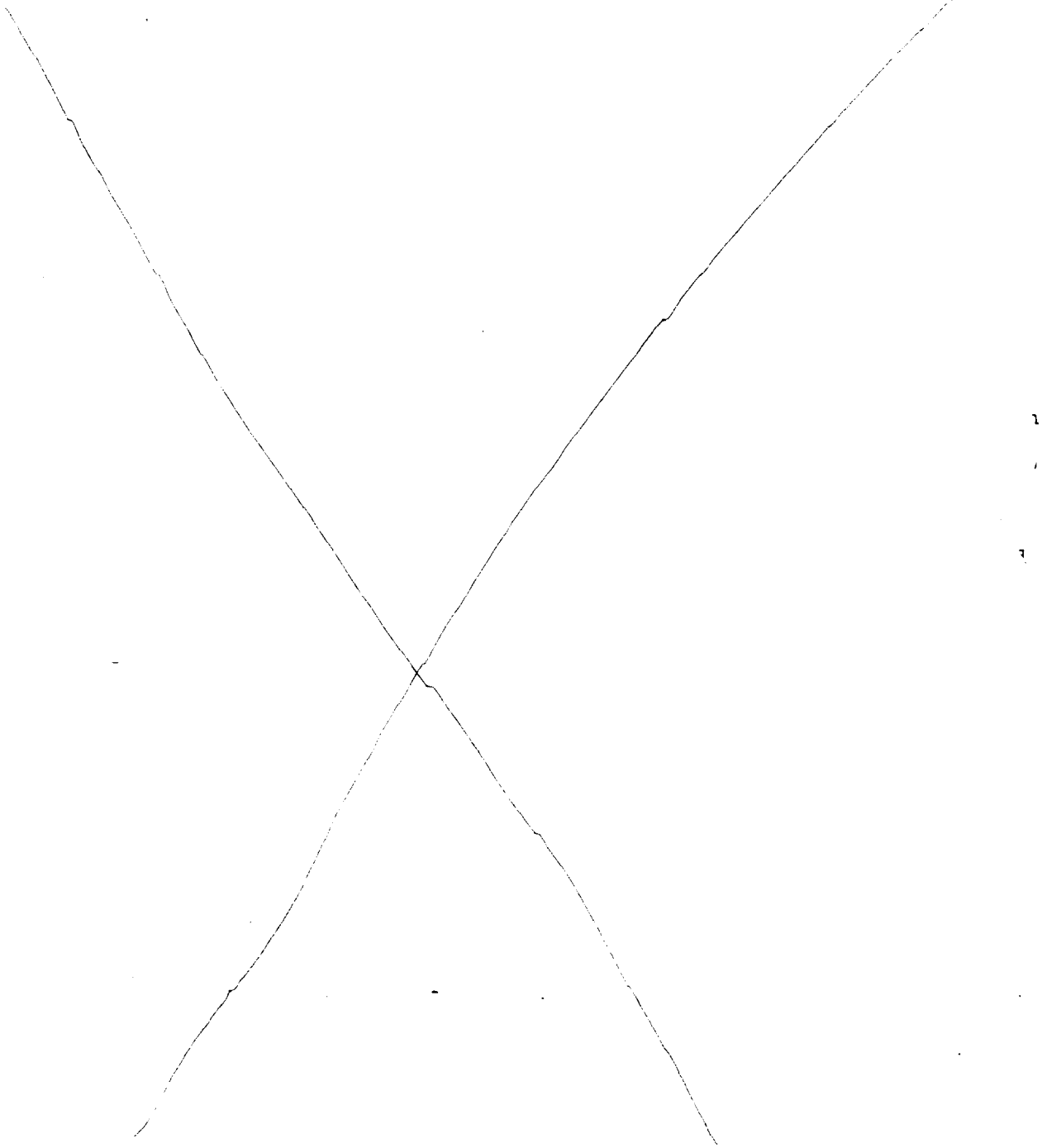
The major process solutions and chromatography gels are listed below. Buffers are prepared with water for injection (WFI), tested for endotoxin and 0.2 micron filtered). In addition, the buffers for the final concentration/diafiltration and formulation are filtered through a molecular weight cutoff membrane . The and Chromatography gels, and cleaning and sanitizing solutions are listed separately.

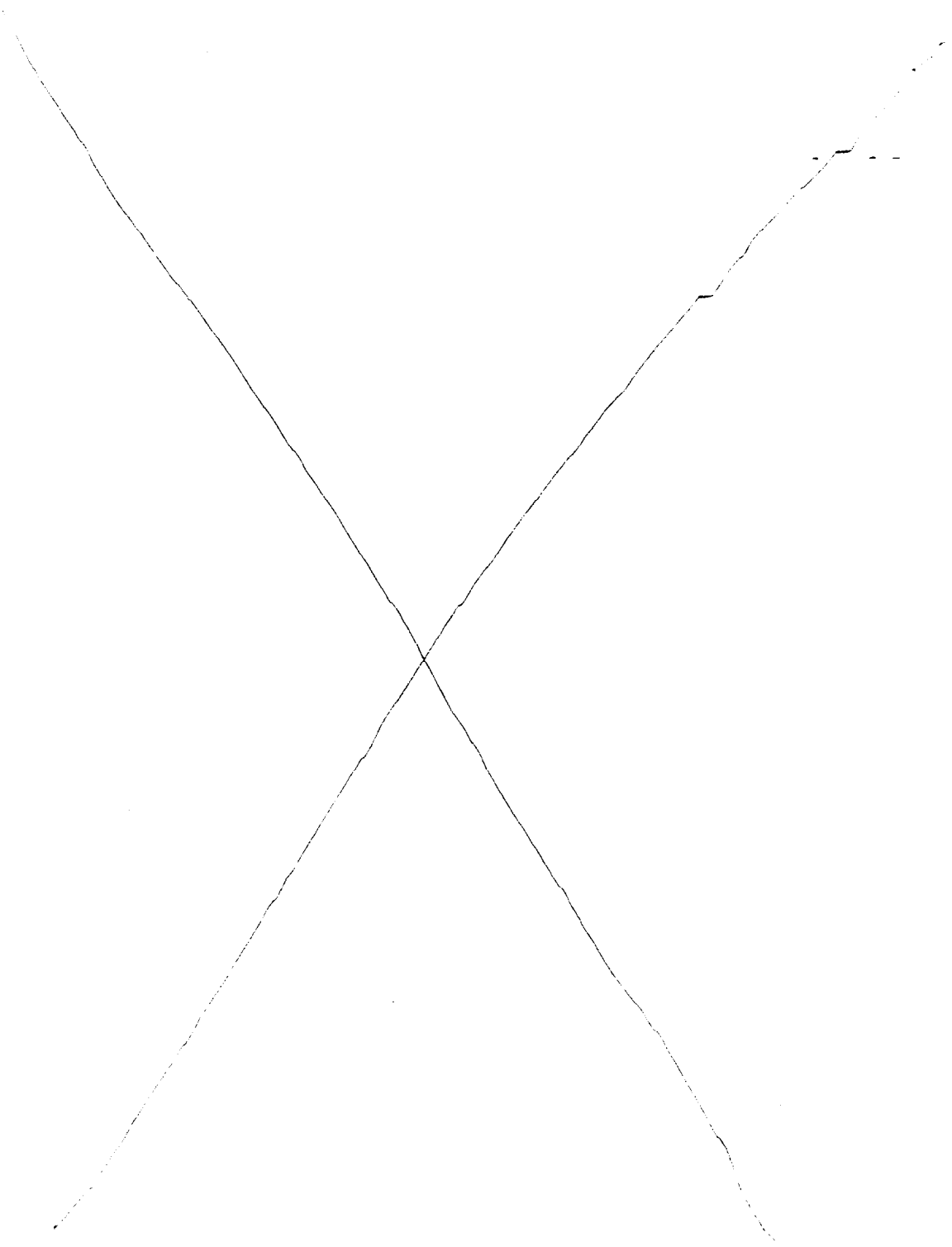


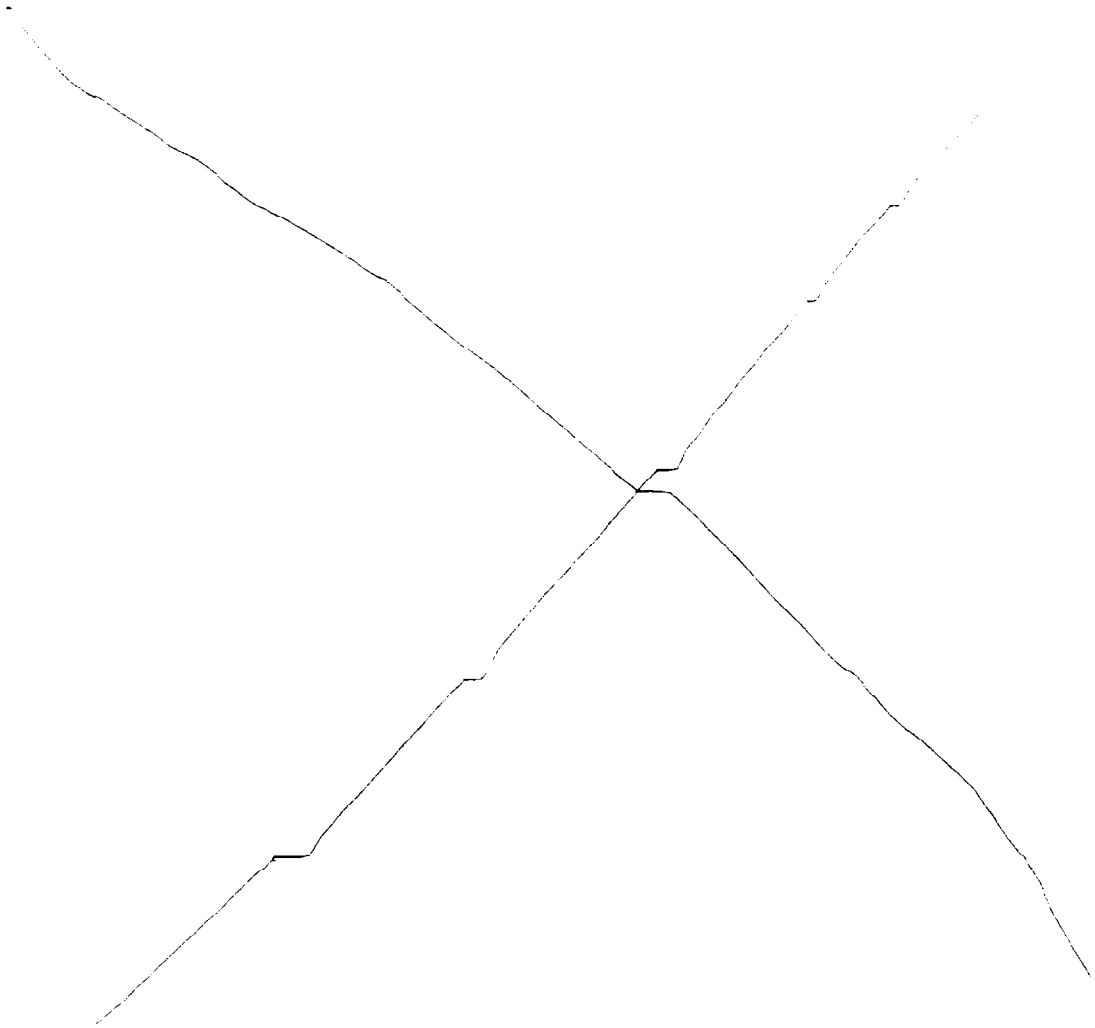
Purification Process Description

(BLA Section 4.2.3.6.2)

The MEDI-493 process consists o— chromatography steps using different separation techniques, a — treatment, and a — step for virus removal. The chromatography consists of a cation exchange capture step, a — affinity chromatography step, a — anion exchange step and a — Each of the process steps has been optimized for operation at room temperature (20 ± 5° C). — includes a — wash to remove process contaminants. A separate — treatment is used as a viral inactivation step. The formulation into — buffer is a multiple step process







Methods to Transfer Product Between Steps

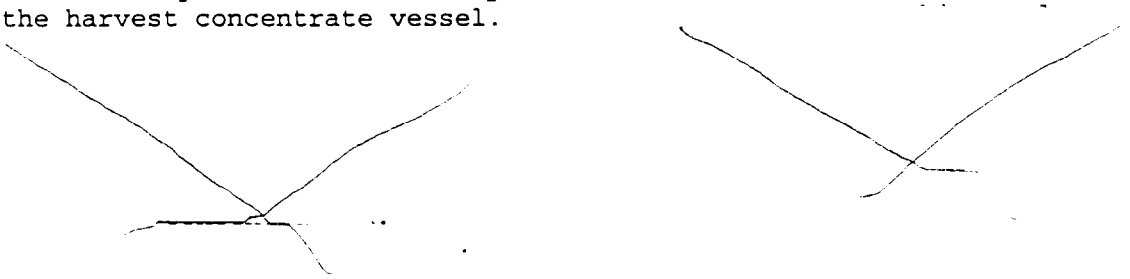
Following pH and conductivity adjustment, the cell-free conditioned medium is transferred from the harvest tank located in the [redacted] 2E [redacted] hromatography column located in Purification Room [redacted] L stainless steel pipe pass-through connection located between the rooms. The transfer is made using a silicone line attached from the harvest tank in Room [redacted] to the stainless steel pipe pass-through. The transfer continues from the pipe pass-through to the silicone load line attached to the load inlet valve on the chromatography controller in Room [redacted] Prior to the inlet valve there is a pre-filter and a 0.2 micron final filter. The controller is connected by silicone tubing to the [redacted] atography column. The [redacted] uct is collected directly into a closed product vessel using silicone tubing connected to a dedicated outlet valve on the chromatography controller. The outlet tubing attaches to a filter housing containing a 0.2 micron filter mounted on the collection vessel. Except for the outlet tubing which is cleaned and autoclaved prior to use, tubing is dedicated to the chromatography controller and is cleaned as part of the controller [redacted]. Transfer to each subsequent chromatography step is carried out by connecting silicone tubing from a diptube or a bottom drain valve of the product vessel to the inlet port on the chromatography controller. In each case the load inlet tubing is silicone, dedicated to the chromatography controller, and cleaned as

part of the controller. Chromatography products are collected directly into a closed product vessel through a filter housing containing a 0.2 micron filter mounted on the collection vessel. The silicone outlet tubing attaches to a dedicated outlet valve on the chromatography controller. This tubing is cleaned and autoclaved prior to use.

[redacted]roduct is[redacted] using autoclaved silicone tubing connecting the product tank bottom valve to th[redacted] nanofilter inlet. The permeate tubing is autoclaved silicone tubing which is attached on one end directly to the permeate end of the [redacted] The other end of the permeate tubing is attached to a filter housing containing a 0.2 micron filter mounted on the collection vessel. The tubing and connections are in place during cleaning and equilibration of the [redacted] filter prior to use [redacted]). The tubing is connected to the product vessel after the equilibration so that the product is not diluted by the equilibration buffer. [redacted] addition of the [redacted] solution into the [redacted] product during the [redacted] treatment step is carried out using silicone tubing connected from the glycine solution vessel to a diptube located on the product vessel. A peristaltic pump is used for the transfer. The same tubing and pump are used for the subsequent addition of neutralizing solution. The silicone tubing is cleaned and autoclaved prior to use.

Process intermediates are stored at 20 + 5° C in Room [redacted] between the chromatography and [redacted] process steps. Upon completion of the viral clearance process steps in purification Room [redacted] the [redacted] product is manually transported in a closed vessel from Room [redacted] through the Staging Room [redacted] the Buffer Preparation Room [redacted] he Staging Room [redacted] then into the second Purification Room [redacted] product vessel is [redacted]d down with [redacted] prior to transfer to personnel inside Room [redacted] Personnel from Room [redacted] may not follow the product through the door into Room [redacted].

The transfer of the [redacted] from the product vessel into the diafiltration tank is done through a 0.2 micron filter using autoclaved silicone tubing and aperistaltic pump. The diafiltration tank is attached to the ultrafiltration skid by silicone tubing. The retentate tubing, which carries the retentate stream back to the diafiltration tank and the permeate tubing which carries the permeate stream to waste collection are also silicone. The inlet, retentate, and permeate lines are dedicated to the ultrafiltration skid and cleaned as part of the system [redacted] tubing used to harvest the concentrated product is autoclaved silicone tubing which connects the ultrafiltration skid to the harvest vessel. The harvest tubing is replaced for each product lot. The concentrated/diafiltered formulated product is initially collected through the retentate tubing into the harvest concentrate vessel.



Inside the Class 100 hood, the formulated product is transferred by air pressure through a 0.2 micron filter into the [redacted] bag. The

Computer Controlled Systems

The chromatography controller equipped with a programmable logic controller (PLC) and software. This instrument monitors pH, conductivity, pressure, flow rate, UV absorbance, flow path and valve actuation in real time during a chromatography step. This instrument is currently used manually. The validation of the software and the equipment used in MEDI-493 production are described in Sections 15.3 and 15.7.1.

Biological Waste Handling

All liquid waste from the pre-viral clearance area is discharged through the floor drains to a validated waste treatment system using greater than 5 parts per million sodium hypochlorite for at least 30 minutes. The treatment product is then neutralized prior to release into the sanitary sewer. All liquid waste streams from the diafiltration/concentration step in the post-viral clearance area are discharged into the sanitary sewer. Solid waste is collected in biohazard waste bags and removed from the facility by a licensed medical waste management contractor.

Drug Product

3)

Composition

The MEDI-493 is a monoclonal antibody which is prepared as a lyophilized product. Prior to use, it is reconstituted with of water for injection (WFI). The pH of the reconstituted MEDI-493 is For lyophilization, the MEDI-493 is formulated with excipients consisting of mannitol, histidine and glycine which are described in detail in Section 4.3.2. The calculated total weight of the dry solids is mg per vial. The calculated dry weight composition and component concentration in the reconstituted product are summarized in BLA Table 4.3.1-1.

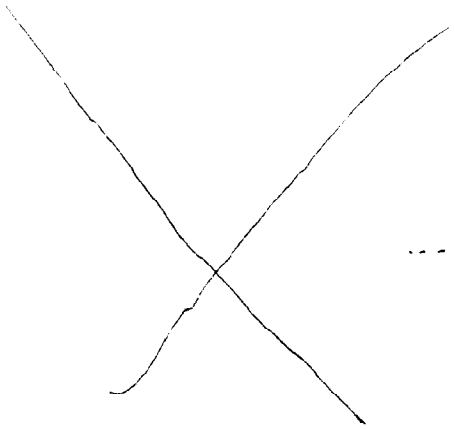
BLA Table 4.3.1-1

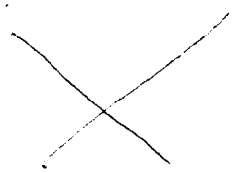
Component	USP	Calculated Dry Weight (mg)	Calculated Concentration after Reconstitution
MEDI-493	NA	120.2	100 mg/mL
Mannitol	USP	67.5	5.6%
Histidine	USP	8.8	47 mM
Glycine	USP	0.2	3.0 mM

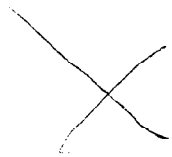
NA = not applicable

The active ingredient in the drug product is the drug substance which is specified in Section 4.2. Excipients used in the MEDI-493 final formulation are USP 23 grade compendial materials. Excipients are tested for identity and released prior to use.

Drug Product Manufacturer



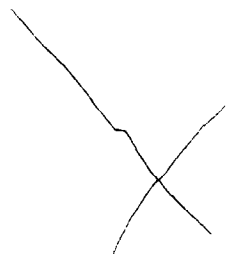


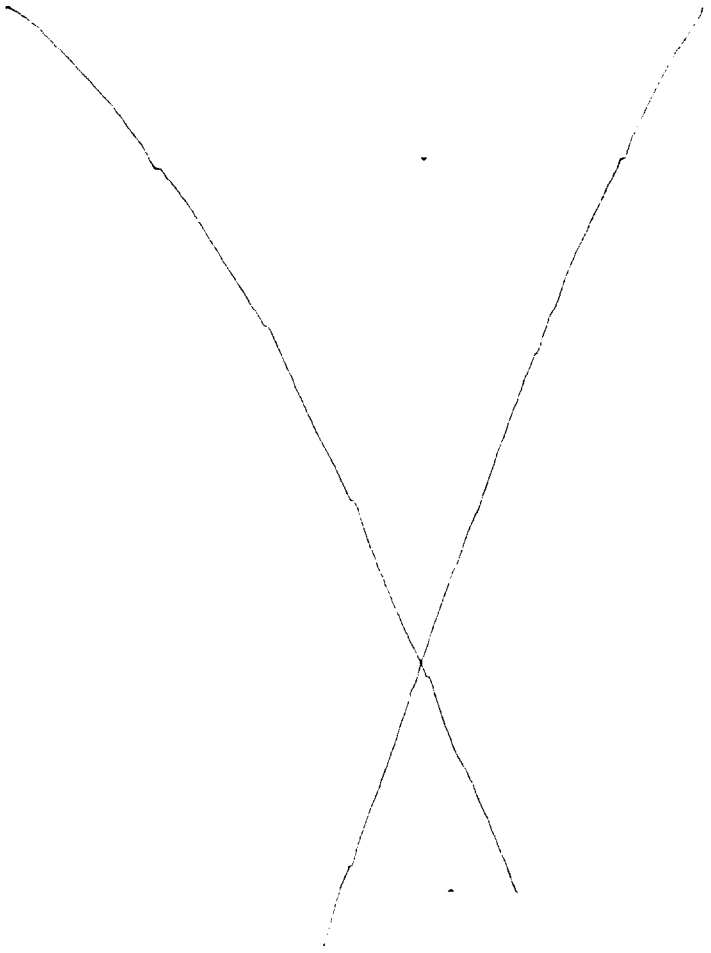


Methods for Fill/Finish and Packaging

Master Production and Control Records (MPRs) describe the manufacturing procedures and specifications for these operations and are included in the Appendix Section 4.3.4.3.1. The MPRs are entitled

The description of the container/closure system for the drug product is presented in Section 4.3.6.





Viral Safety

Overview of Viral Safety

(from Process Overview Section 3.4.2)

Several approaches are used to assess and ensure viral safety of MEDI-493 (Sections 4.2.3.4, 4.2.3.5, 4.2.3.6, 4.2.4.2.2). This includes restricted sourcing and testing of bovine-derived cell culture medium components, exclusion of human, bovine, or porcine derived components from the purification process, characterization of the MCB, WCB, and End of Production(EOP) cells, measurement of the viral clearance capability of the purification process, and final product testing.

There are no materials of human or porcine origin used in either the cell culture or purification process, and no bovine products used for MEDI-493 purification. The [redacted] and [redacted] used in the purification process are recombinant proteins produced in E. coli. The cell culture medium contains [redacted] bovine products: [redacted] The [redacted] used in the cell culture medium is recombinant [redacted] produced in yeast. To ensure that the risk of transmitting bovine spongiform encephalopathy is reduced to the lowest possible level, all [redacted] bovine products are obtained from either US or Canadian sources which are considered to be BSE-free by the United States Department of Agriculture and the European

Community. Risk assessment calculations show that for all ——— bovine-derived components the margin of safety exceeds the recommended safety level established by the German Federal Ministry of Health in "Decree for the Protection of Consumers Against Bovine Spongiform Encephalopathy, 1996." The MCB was shown to be virus-free when tested for mouse antibody production, in in vivo and in vitro assays for adventitious viruses, in an extended S+L- focus assay, and in an extended XC plaque assay. The WCB was also demonstrated to be free of viral contamination when tested in in vivo assays for adventitious viruses. Testing of the EPC revealed no evidence of viral contamination using the mouse antibody production test, or in vivo and in vitro assays for adventitious viruses. Negative stain electron microscopy revealed Type A and Type C retroviral particles in EPC samples ranging from articles/mL. The EPC samples containing these retroviral particles were further tested by the S+L- focus forming and XC plaque assays, and in these tests no evidence of retroviral contamination was detected. The EPC samples were also characterized by a co-cultivation assay using a human rhabdomyosarcoma and a mink lung cell line. An endpoint S+L- focus forming assay and a reverse transcriptase assay confirmed the absence of infectious retroviral particles in both the human and mink cell lines. The co-cultivation assay was also performed on the drug product and yielded negative results.

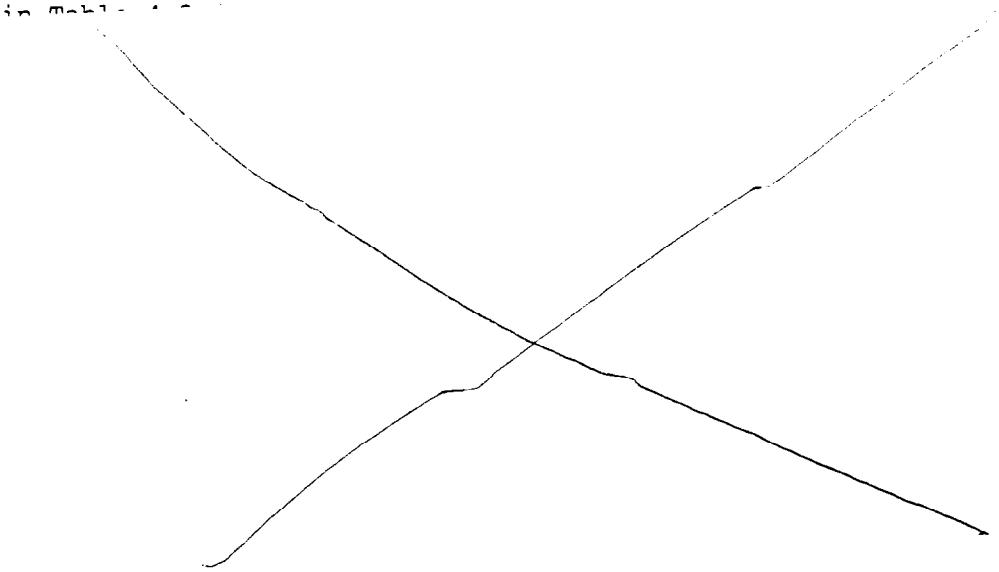
Viral Clearance

(from BLA Overview Section 3.4.2 and Section 4.2.4.2.2.2)

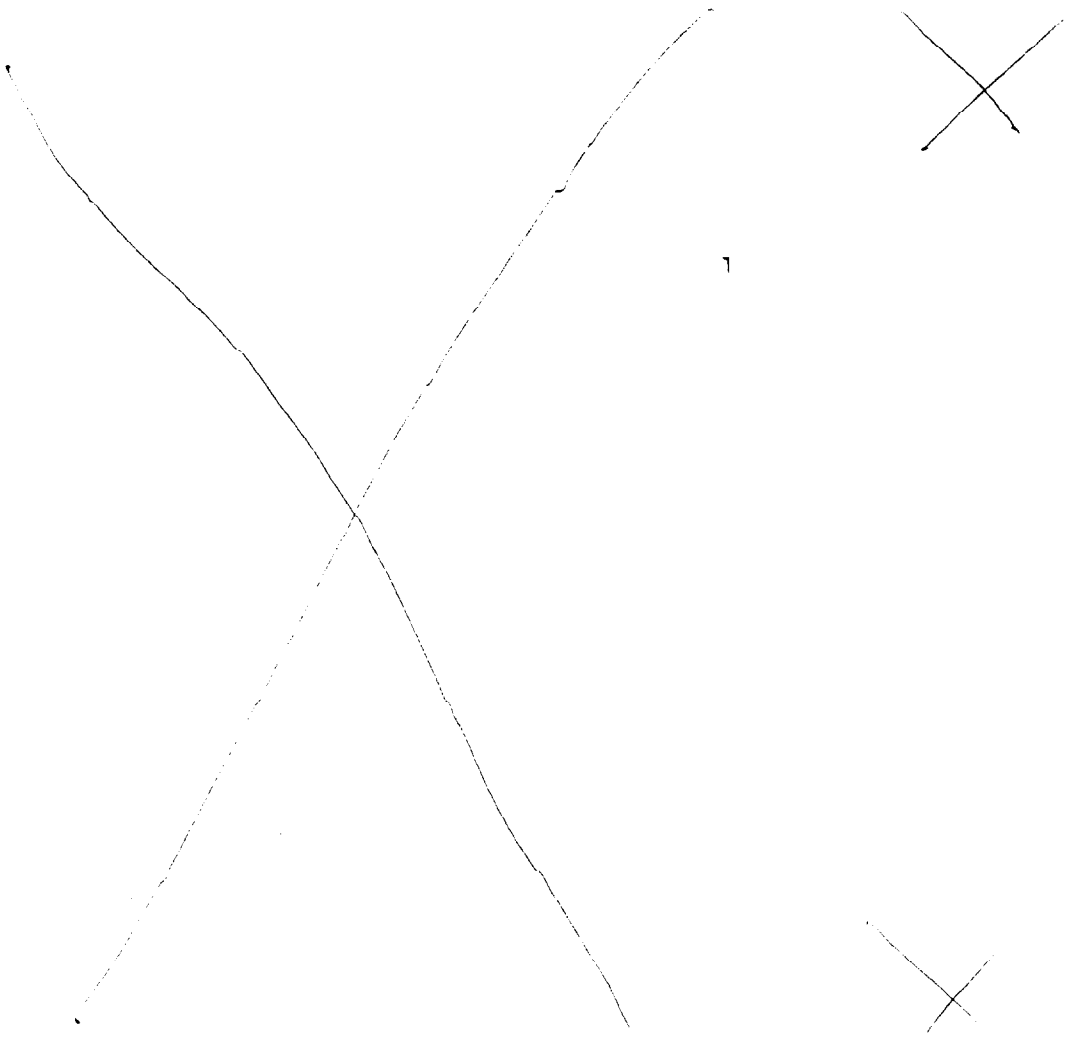
Viral clearance studies were undertaken to assess the ability of each purification process step to remove or inactivate four model viruses

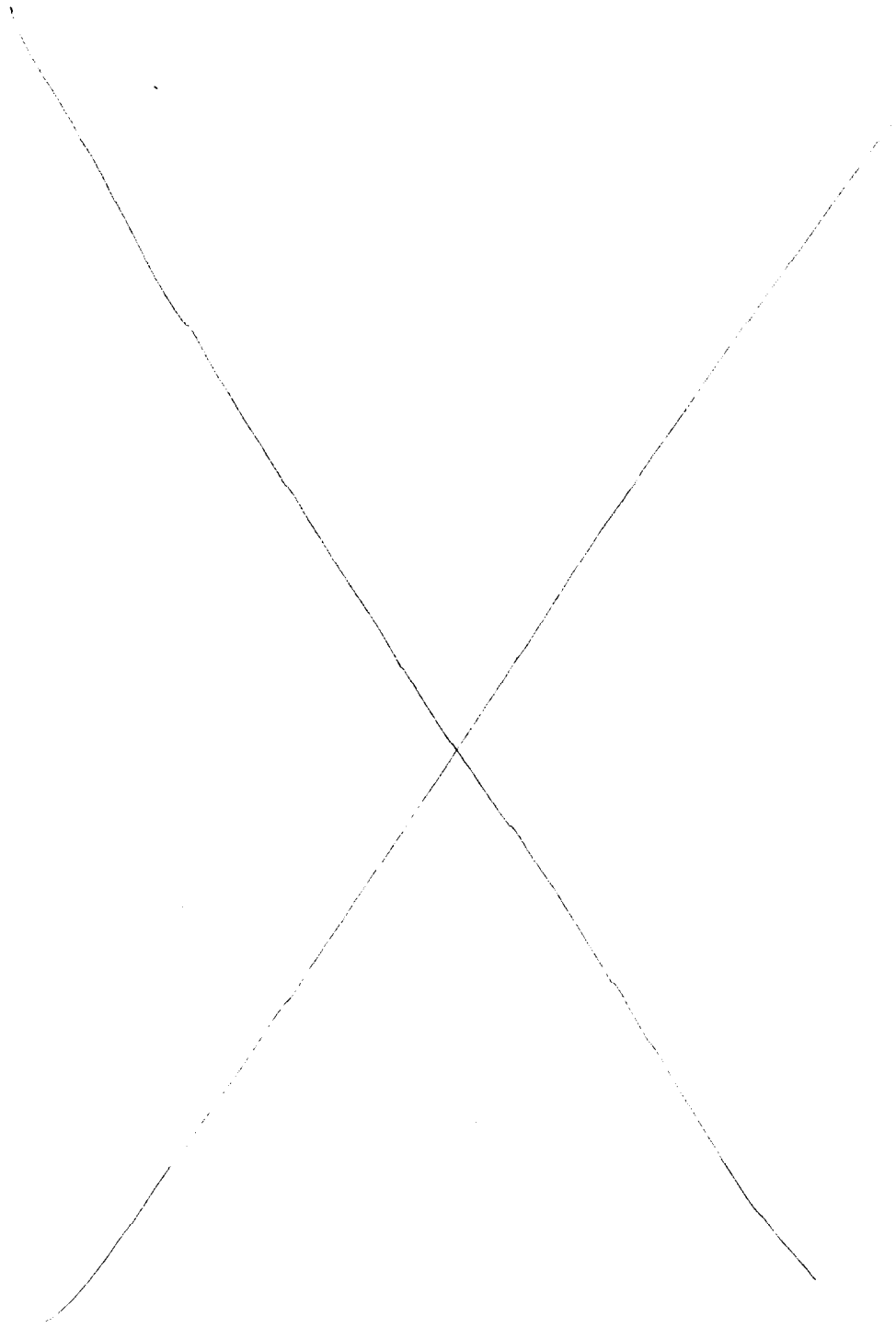
For the viral clearance study, each step of the process was scaled down relative to the process scale used for the manufacture of the Phase III production material times greater

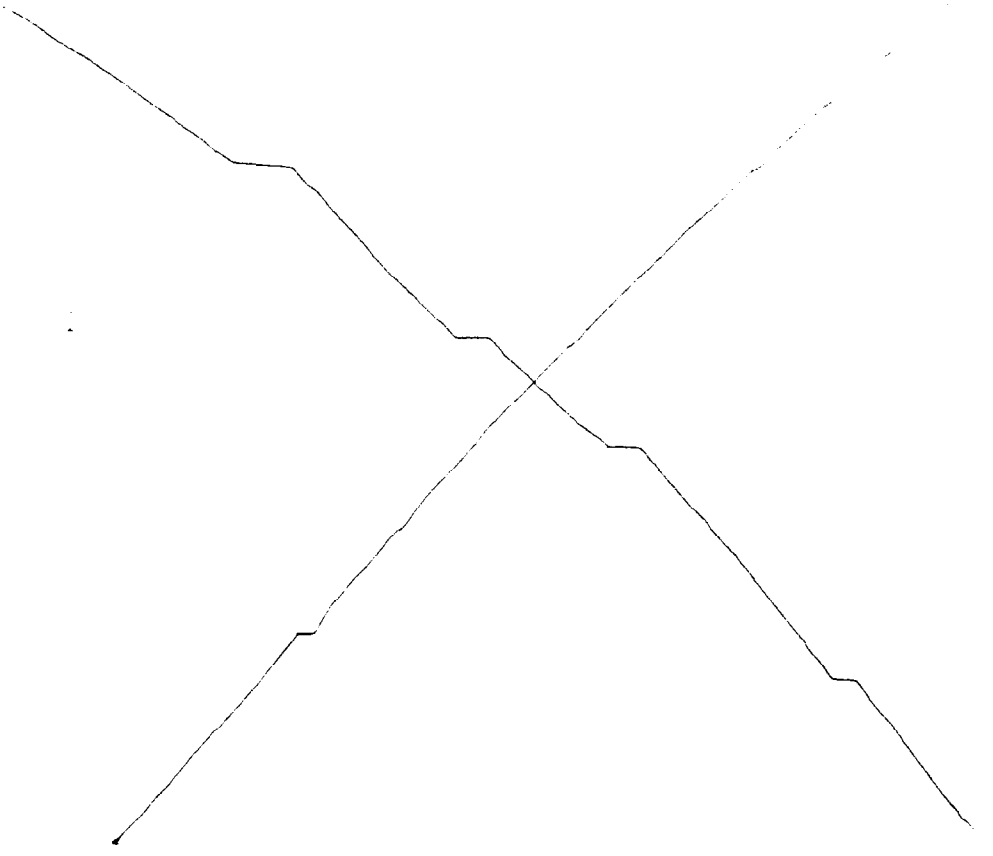
the buffer conditions, temperature, protein concentrations and process parameters used in the clearance study were designed to be as close to the Phase III process parameters as possible. The column sizes were designed to keep the bed heights and the linear flow rates within a factor of and other operational parameters such as g protein/L gel as close as possible to those used in manufacturing.
Phase III scal



Step $\log_{10}$ reduction = (total $\log_{10}$ PFU or FFU in load) - (total $\log_{10}$ PFU or FFU in product)







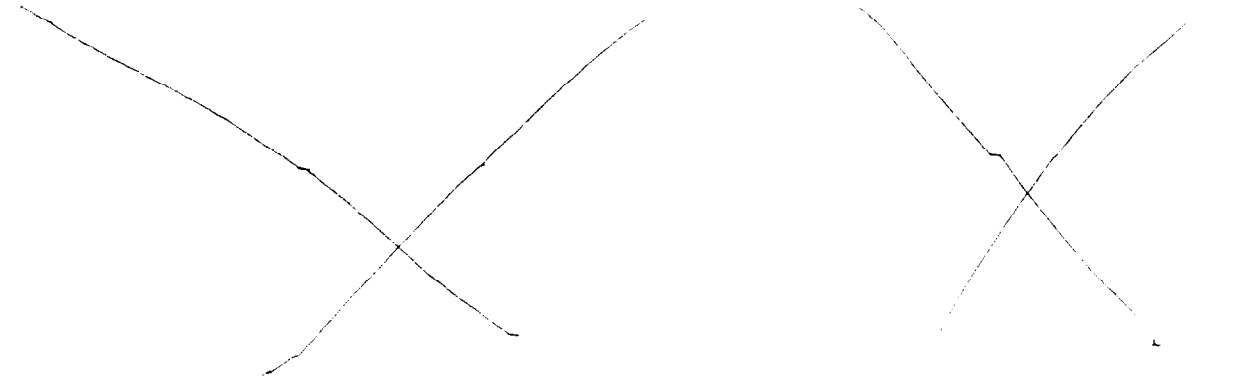
Containment and Contamination Precautions

Various precautions are taken to ensure product integrity and prevent contamination during production (Section 4.2.2.3). The product manufacturing areas and personnel are dedicated on a single product campaign basis, and only qualified personnel are permitted to work in the manufacturing facility. Separate gowning areas are provided for cell culture and purification. Prior to entry into the production areas, personnel put on hair covers, face masks, gloves, sterile gowns and shoe covers. In addition, a full hood and double sterile gloves are required for bulk filtration operations. There are no other cell lines or products present in the MEDI-493 production area throughout the duration of MEDI-493 manufacturing, and at the current time, there is no plan to introduce other products into the [redacted] production equipment such as glassware, bioreactors, columns and tanks are dedicated to MEDI-493 use. Portable product contact equipment are identified with product-specific labels. The equipment is cleaned according to validated procedures (Section 15.3), visually inspected prior to use, and the status of each piece of equipment is labeled throughout the operations. Product contact surfaces of process equipment and piping are constructed of 316L stainless steel and fabricated according to sanitary design standards. Clean-in-place and steam-in-place procedures are employed to ensure the cleanliness and sterility of equipment.

Cleaning validation studies have been undertaken to verify effectiveness of the cleaning procedures used and to assure that process contaminants do not accumulate on the product contact surfaces (Section 15.3 and 15.4). The sterilization of cell culture medium and the drug substance are performed according to validated procedures (Sections 4.2.4.2.3). The cleanliness of production areas is maintained by performing routinely scheduled cleanings.

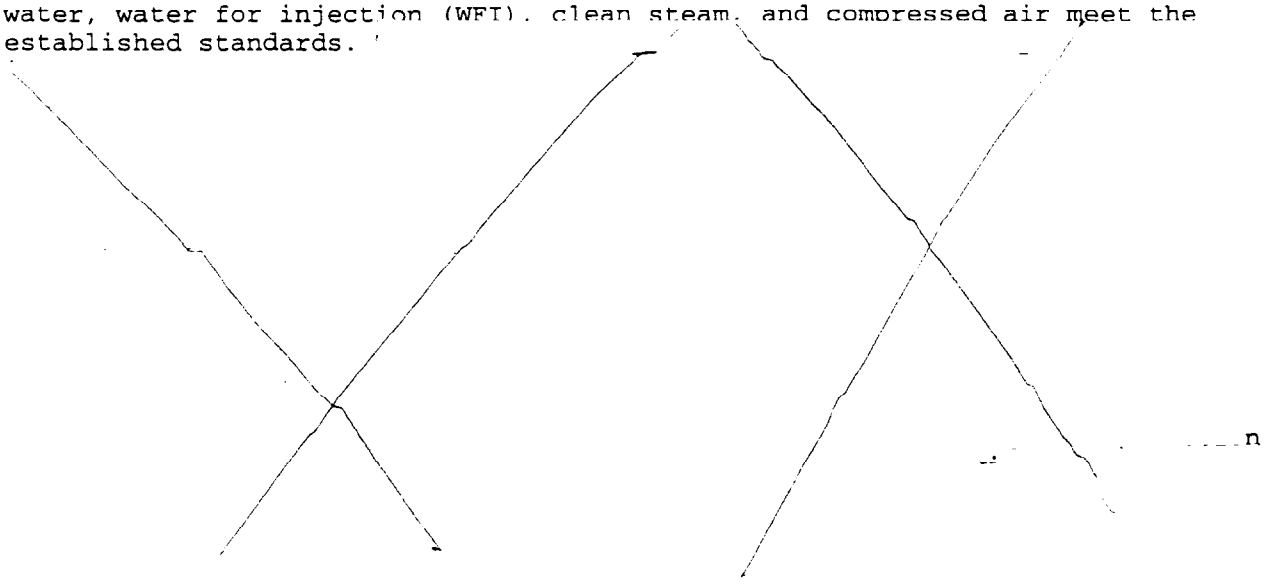
Disinfectants are rotated for ceiling, wall, and floor cleaning to control bacterial and fungal growth in the production environment. Effectiveness of cleaning is assessed by the environmental monitoring program previously described. The media preparation, inoculum expansion, and bioreactor operations are conducted in Class 100,000 areas, and any open manipulations (e.g. small scale media filtrations and sampling and splitting of cultures) are performed in a Class 100 biological safety cabinet BSC) under laminar flow HEPA-filtered air. When performing open manipulations aseptically in the BSC, personnel put on sterile gloves and spray the gloves with 70% alcohol between steps to minimize the risk of contamination. The work surface of the BSC is cleaned and disinfected with 70% alcohol before use. Large scale media filtrations are performed at the receiving bioreactors, and the 0.2 µm filters, transfer lines, and receiving bioreactors are steam-sterilized prior to the transfers. The integrity of the 0.2 µm filters are verified after the filtrations. The bioreactors and the harvest tank were validated to be closed systems. The vessels are equipped with steam-sterilizable ports for aseptic sampling and addition of inoculum, media, and nutrient feeds. The flexible transfer line between the expansion bioreactor and the production bioreactor is steam-sterilized in place prior to transferring the culture. The inlet (headspace and sparger) and exhaust gases are sterilized by 0.2 µm hydrophobic filters. The integrity of the 0.2 µm filters are verified after each use. A positive vessel pressure is maintained during media hold and cultivation of cells. All product contact O-rings, gaskets, and seals are cleaned and inspected after each run. As in-process controls, T-flasks and spinner flasks are visually inspected daily for signs of contamination, and bioreactor cultures are aseptically sampled and microscopically examined for microbial contaminants. The absence of viral or microbial contamination in bioreactor cultures is further verified in EPC characterization studies (Section 4.2.3.4.3).

Several types of contamination precautions are used to protect the product during purification. This includes precautions to minimize potential exposure to adventitious agents, and to segregate process steps according to pre- and post-viral clearance (inactivation and removal).



Quality Control Testing

Quality Control (QC) testing is conducted throughout the MEDI-493 manufacturing operation. This includes environmental monitoring; and testing of critical utilities, raw materials, in process samples, drug substance, and drug product. In addition, procedures are in place to qualify reagents, standards, and controls ——— Section 15.9.4), and for testing of samples and reporting of results (Section 15.9.4; and——— and Section 15.9.8, respectively). Re-analysis of samples that have failed test specifications is proceduralized ———, Section 15.9.7) to ensure that the re-analysis is only performed under defined and controlled conditions. Critical Utilities and Environmental Monitoring Routine testing is performed to ensure that critical utilities such as reverse osmosis de-ionized (RODI) water, water for injection (WFI), clean steam, and compressed air meet the established standards.



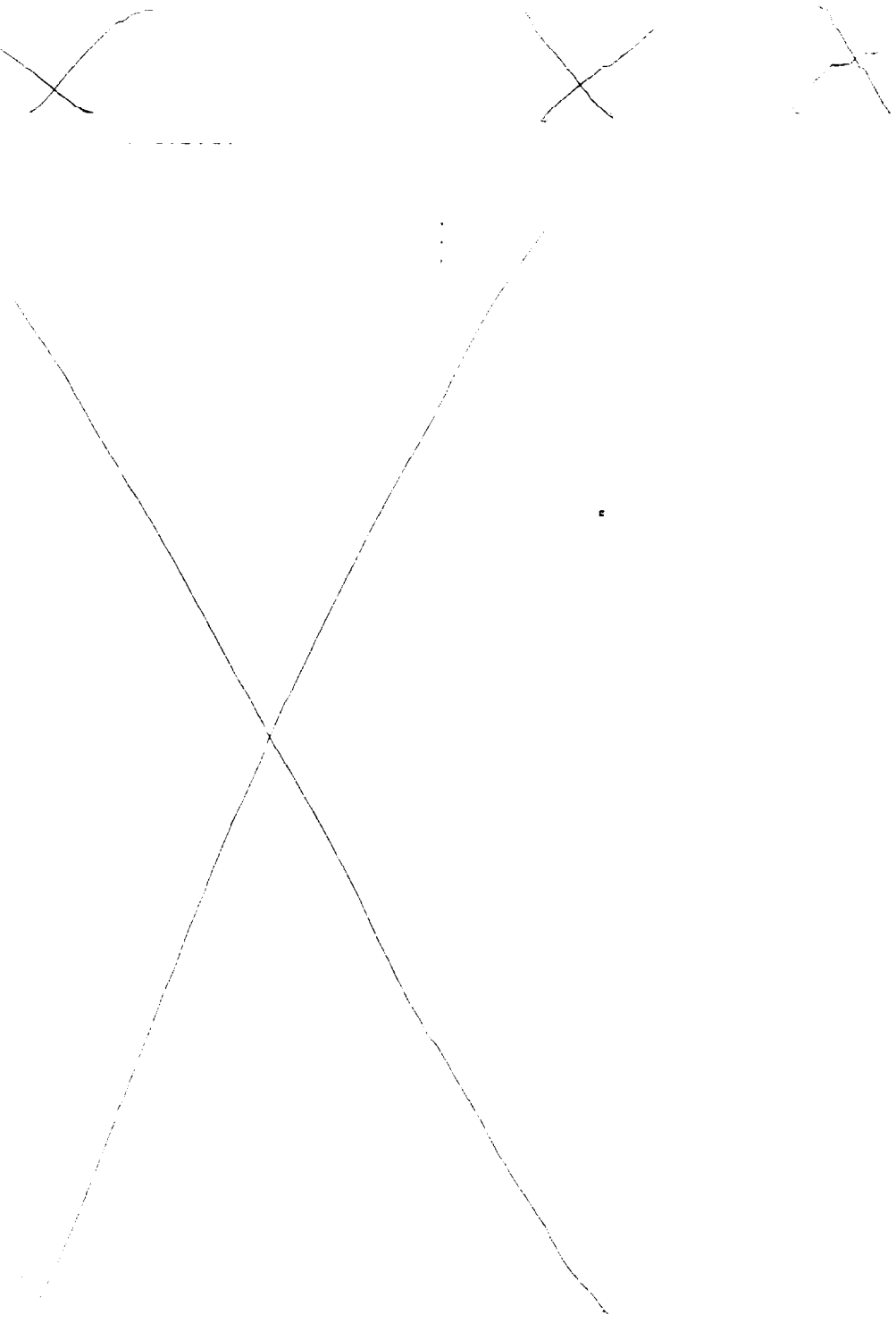
Raw Material Testing

Incoming raw materials including product contact disposables are tested by either the QC department or the component manufacturer (Section 4.2.3.1). QC selects the appropriate tests for each item based on the use and origin of the item. A manufacturer's certificate of analysis (CoA) is required for each raw material. An appearance test is performed on product contact disposables. Testing performed on other raw materials includes an identification test and when appropriate, a suitability for use test. When available, compendial methods are used for testing (Section 4.2.3.1.2). Raw material test results are recorded on appropriate data capture forms which are part of the SOP's. Material that does not meet specification is re-tested———— and if rejected is not used for manufacturing.

In-Process Testing and Controls

In-process testing is conducted by both the QC and manufacturing groups (Section 4.2.4.1). Tests conducted by manufacturing include determination of cell concentration and viability, filter integrity, visual inspections for contamination, pH, and tests to evaluate operating parameters of equipment and other related measures of process performance. Tests conducted by QC support both cell culture and purification operations. These tests include endotoxin and bioburden tests for evaluation of microbial contamination in the process stream. QC testing also includes tests to characterize the product throughout the manufacturing process, and to demonstrate removal of process contaminants

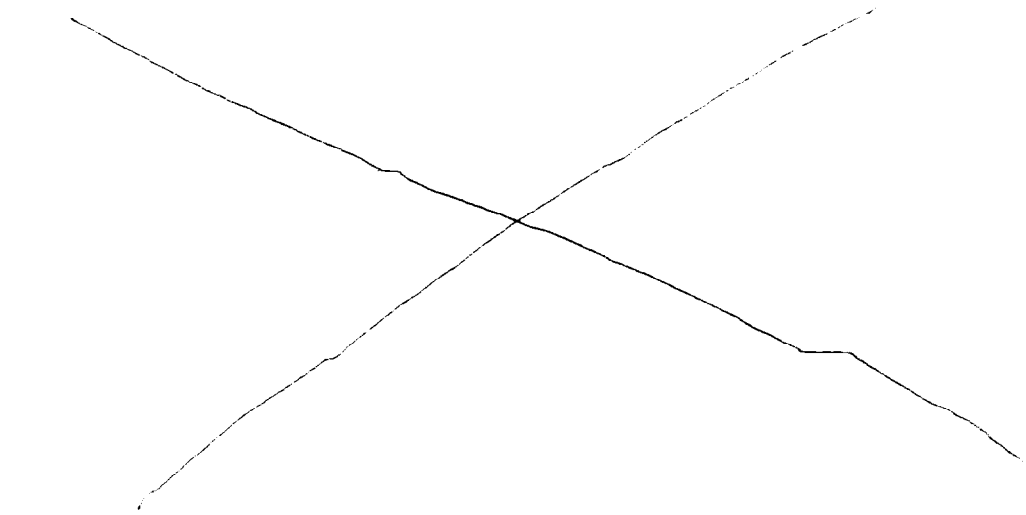
by the purification steps. Product characterization tests include reducing and non-reducing SDS-PAGE, high performance size exclusion chromatography, the n ELISA, reducing isoelectric focusing and quantitation of MEDI-493. Tests for detection of residual amounts of process contaminants include assays



Drug Substance Testing

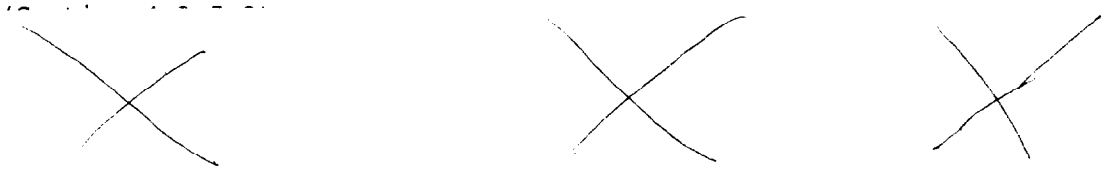
Testing is conducted on the drug substance to ensure that it is suitable for use. These tests include total protein, ELISA, SDS-PAGE (reducing and non-reducing), reducing IEF, high performance [illegible] chromatography, endotoxin, and sterility

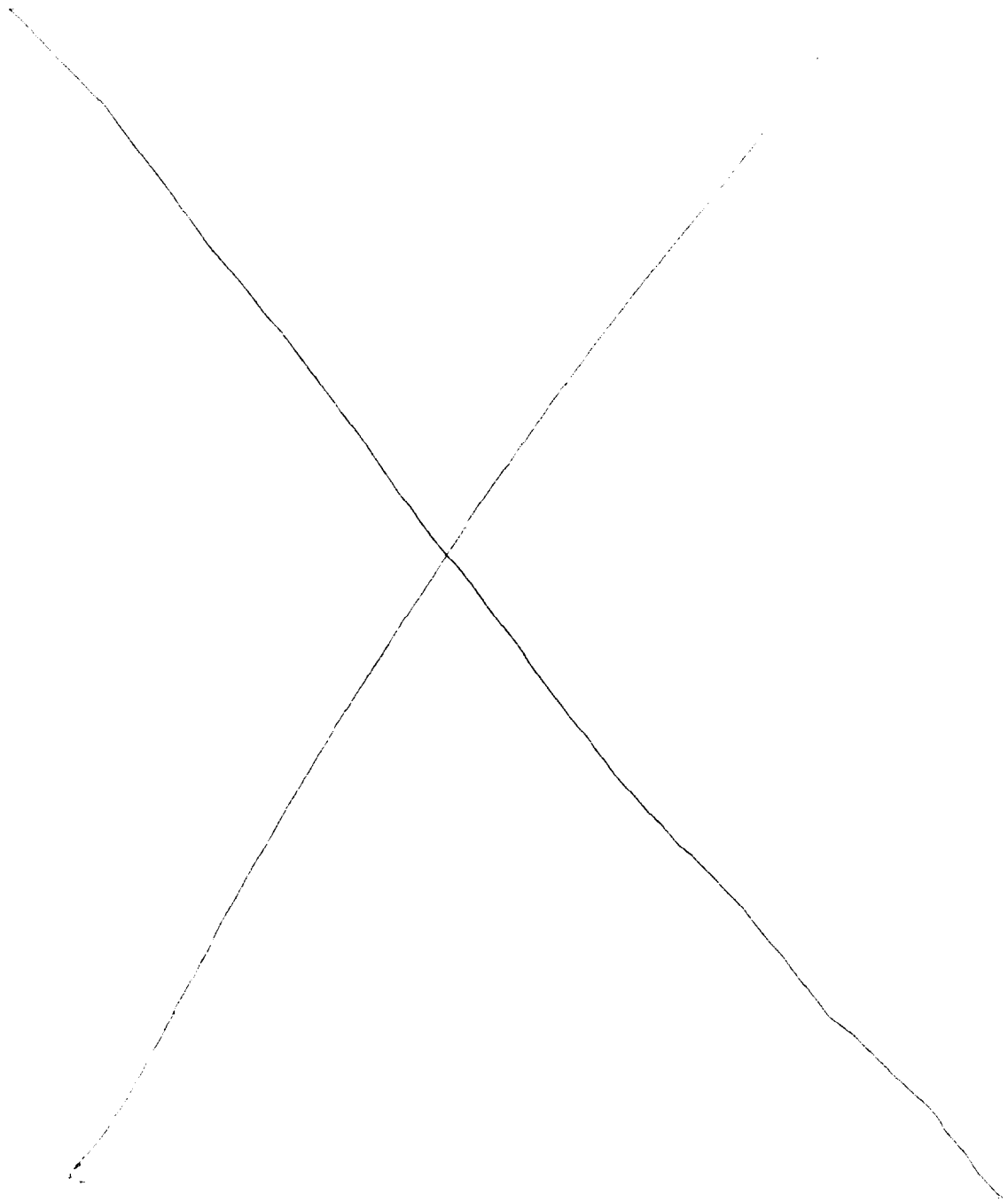
a brief descript[illegible]



Drug Product Testing

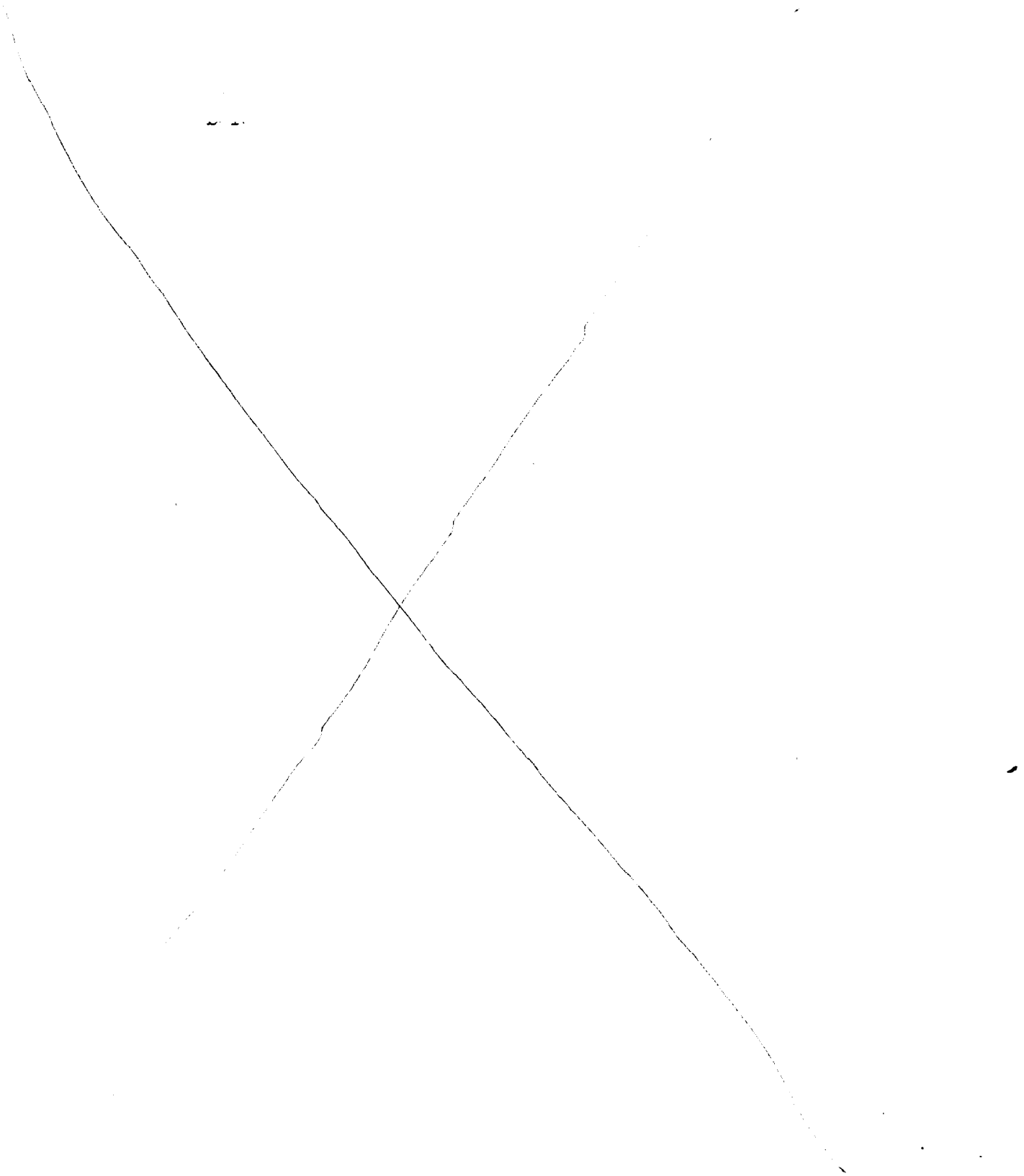
Testing is conducted on the drug product to ensure it is suitable for use. These tests include total protein, [redacted] ELISA, SDS-PAGE (reducing and non-reducing), reducing IEF, high performance size exclusion chromatography, appearance (both lyophilized and reconstituted product), pH, moisture content, endotoxin, and sterility (Sections 4.3.5 and 6.0). Specifications for the various assays were set based on historical product experience and current regulatory guidelines. The consistency lots [redacted] pass the specifications set for all lot release tests





Impurity Testing

Testing is conducted on the drug substance and on the steps immediately prior to formulation to determine if residual amounts of process contaminants are at acceptable levels.



Stability

Overview

(from the Process Overview section of the BLA 3.4.4)

Stability programs are in place for both MEDI-493 drug substance and drug product. The stability program is described in ——————which is found in Appendix Section 4.2.8.8.2. MEDI-493 drug substance stability data indicate that MEDI-493 is a robust and stable molecule (Section 4.2.8). Data collected for storage at 2-8°C (up to 9 months), 15-25°C (up to 2 weeks), and -70 to -80°C (up to 2 years) passed specifications indicating that MEDI-493 is stable under these conditions for at least these time periods. Evaluation of MEDI-493 stored at 38-42°C demonstrated that the molecule can withstand elevated temperature conditions for ≤ 3 days and remain within testing specifications. The data also show similar stability profiles for MEDI-493 prepared at different manufacturing scales. To further evaluate drug substance stability the three consistency lots were placed on stability in scaled-down storage bags (three lots, stability protocol ——————) and in a scaled-down stainless "316L" steel container (one lot, stability protocol ——————) for a minimum of 6 months with interim time points at 1, 2 and 3 months.

The drug substance is evaluated for stability, contamination, strength, potency and purity using the following assays: appearance, total ——————protein binding ELISA, microneutralization, SDS-PAGE (reducing and non-reducing), reducing isoelectric focusing,

Drug product consistency lots were placed on stability as described in stability protocol [redacted] (Section 4.3.8). The lots are tested at time intervals of 1, 2, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months at both the recommended storage temperature of 2-8°C and at an elevated temperature of 20-24°C. Additional excursion conditions are evaluated at 1, 2, 3, and 6 months. These include storage at 38-42°C, short-term exposure to high intensity light or heat (38-42°C) followed by return to normal (2-8°C) conditions, and repeated freeze thaw cycles of product with return to normal conditions. As described in stability protocol SP-0009, the initial time point results will be the drug product lot release data. The time points after the initial point are determined from the time the product is placed at a given condition (e.g., 20-24°C or 38-42°C). The drug product is evaluated for stability, contamination, strength, potency and purity using the methods described above for the drug substance. In addition, it is also evaluated for moisture content by Karl Fischer analysis, container integrity, particulate matter, and sterility (Sections 4.3.5, 4.3.8 and 6.0). Historical stability data, and stability data collected on the consistency lots and future lots will be used to further determine the time and temperature limits for drug product storage. Future lots of drug product to be placed on stability are described in [redacted] In conclusion, the data to date support expiration dating of two years when MEDI-493 drug product is stored at 2-8°C.